HIGH PRODUCTION VOLUME (HPV) CHALLENGE PROGRAM

TEST PLAN
FOR
2,2,4-TRIMETHYLPENTANE-1,3-DIOL
(CAS NO.: 144-19-4)

PREPARED BY:

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OVERVIEW

The Eastman Chemical Company hereby submit for review and public comment the test plan for 2,2,4-trimethylpentane-1,3-diol (TMPD; CAS NO.: 144-19-4) under the Environmental Protection Agency's (EPA) High Production Volume (HPV) Chemical Challenge Program. It is the intent of our company to use existing data on TMPD in conjunction with EPA-acceptable predictive computer models to adequately fulfill the Screening Information Data Set (SIDS) for the physicochemical, environmental fate, ecotoxicity test, and human health effects endpoints. We believe that in total these data are adequate to fulfill all the requirements of the HPV program without need for the conduct of any new or additional tests.

TMPD is a solid, white, crystalline material manufactured to a high degree of purity. This compound finds its primary use in industrial applications where it is utilized as a monomer intermediate in the manufacture of various types of polymer resins, polyesters, elastomers, polyols and foams. Applications where TMPD is useful include high-solids industrial baking enamels, laminating resins for fiberglass-reinforced plastics, and thermoset resins for fiberglass-reinforced plastic corrosion-resistant articles.

TEST PLAN SUMMARY

CAS No. 144-19-4	Information	OECD Study	Other	Estimation	GLP	Acceptable	New Testing Required
STUDY	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N
PHYSICAL-CHEMICAL DATA							
Melting Point	Y	-	Y	-	N	Y	N
Boiling Point	Y	-	Y	-	N	Y	N
Vapor Pressure	Y	-	-	Y	N	Y	N
Partition Coefficient	Y	-	-	Y	N	Y	N
Water Solubility	Y	-	Y	-	N	Y	N
ENVIRONMENTAL FATE ENDPOINTS							
Photodegradation	Y	-	-	Y	N	Y	N
Stability in Water	Y[1]	-	-	Y	N	Y	N
Biodegradation	Y	Y	-	-	Y	Y	N
Transport between Environmental Compartments (Fugacity)	Y	-	-	Y	N	Y	N
ECOTOXICITY							
Acute Toxicity to Fish	Y	-	Y	-	Y	Y	N
Acute Toxicity to Aquatic Invertebrates	Y	Y	-	-	Y	Y	N
Toxicity to Aquatic Plants	Y	Y	-	-	Y	Y	N
TOXICOLOGICAL DATA							
Acute Toxicity	Y	-	Y	-	Y	Y	N
Repeated Dose Toxicity	Y	-	Y	-	Y	Y	N
Genetic Toxicity – Mutation	Y	Y	-	-	Y	Y	N
Genetic Toxicity – Chromosomal Aberrations	Y	Y	-	-	Y	Y	N
Developmental Toxicity	Y	Y	-	-	Y	Y	N
Toxicity to Reproduction	Y	Y	-	-	Y	Y	N

1. A technical discussion has been provided.

TEST PLAN DESCRIPTION FOR EACH SIDS ENDPOINT

A. Physicochemical

Melting point - A value for this endpoint was obtained from a textbook reference in the HSDB.

Boiling Point - A value for this endpoint was obtained from a textbook reference in the HSDB.

Vapor Pressure - A value for this endpoint was obtained using MPBPWIN, a computer estimation model in EPI suite.

Partition Coefficient - A value for this endpoint was obtained using KOWWIN, a computer estimation model in EPI suite.

Water Solubility - A value for this endpoint was obtained from a textbook reference in the HSDB.

Conclusion: All end points haven been satisfied by the utilization of data obtained from either the various physical chemical data modeling programs within the EPIWIN suite or from textbook references found within the Hazardous Substance Data Bank (HSDB)(1). The results from the utilization of the models within this program have been noted by the Agency as acceptable in lieu of actual data or values identified from textbooks (2). No new testing is required.

B. Environmental Fate

Photodegradation - A value for this endpoint was obtained using a computer estimation model in EPI suite.

Stability in Water - A technical discussion describing the stability of TMPD in water was provided.

Biodegradation - This endpoint was satisfied through data derived from a study that followed an established OECD test guideline (301A) and was conducted under GLP assurances.

Fugacity - A value for this endpoint was obtained using the EQC Level III partitioning computer estimation model in EPI suite.

Conclusion: All endpoints have been satisfied using actual data or through the utilization of Agency-acceptable estimation models (2). A technical discussion was used to fulfill the endpoint assessing the stability of TMPD in water. In total, they are of sufficient quality to conclude that no additional testing is needed.

C. Ecotoxicity Data

Acute Toxicity to Fish - This endpoint is filled by data from a well-conducted study with acceptable methods and GLP assurances.

Acute Toxicity to Aquatic Invertebrates - This endpoint is filled by data from an OECD TG-202 and EEC/Annex VC.2 guideline study conducted under GLP assurances.

Toxicity to Aquatic Plants - This endpoint is filled by data from an OECD TG-201 and EEC/Annex VC.3 guideline study conducted under GLP assurances.

Conclusion: All endpoints have been satisfied with data from well-conducted studies using acceptable methodologies. While the data from the fish and Daphnia studies were not conducted using standardized OECD guidelines and GLP assurances. These studies are of sufficient quality to conclude that no additional testing is needed.

D. Toxicological Data

Acute Toxicity - This endpoint is filled by data from studies conducted in rats, mice, and guinea pigs following both oral and inhalation exposures. Although the studies did not follow standardized guideline protocols, the quality of these studies was deemed as "reliable with restrictions".

Repeat Dose Toxicity - This endpoint is filled by data from a dietary exposure study in rats of 60-days duration. Although the study did not follow standardized guideline protocols, the quality of this study was deemed as "reliable with restrictions".

Genetic Toxicity

Mutation - This endpoint is filled with a study that followed OECD guideline #471 and was conducted under GLP assurances. This study utilized *Salmonella typhimurium* (strains TA 98, 100, 1535, 1537, and 1538) and *Escherichia coli* (strain WP2*uvr*A). The quality of this study was deemed as "reliable without restrictions".

Aberration - This endpoint is filled with data from an *in vitro* study using Chinese hamster ovary (CHO) cells that followed OECD guideline #473 and was conducted under GLP assurances. The quality of this study was deemed as "reliable without restrictions".

Developmental

Toxicity - This endpoint is filled by data from a dietary exposure study in which rats were fed TMPD for 3 generations. This protocol evaluated both developmental and reproductive toxicity potential similar to that of an OECD guideline #421 study that is a developmental and reproductive toxicity screen. The quality of this study was deemed as "reliable with restrictions".

Reproductive

Toxicity - This endpoint is filled by data from a dietary exposure study in which rats were fed TMPD for 3 generations. This protocol evaluated both developmental and reproductive toxicity potential similar to that of an OECD guideline #421 developmental and reproductive toxicity screen. The quality of this study was deemed as "reliable with restrictions".

Conclusion: All endpoints have been satisfied with data from studies whose methods were very similar to guideline studies or were scientifically appropriate. All studies were conducted prior to the enactment of GLP assurances. In total they were all of sufficient quality to conclude that no additional testing is needed.

SIDS DATA SUMMARY

Data assessing the various physicochemical properties (melting point, boiling point, vapor pressure, partition coefficient, and water solubility) for TMPD were obtained from either text references within the Hazardous Substance Data Bank (HSDB) or estimation models within the EPIWIN suite. These data indicate that TMPD is a solid material at room temperature with a very low vapor pressure. It has a low estimated octanol to water partition coefficient and accordingly is moderately soluble in water.

The assessment of the environmental fate endpoints (photodegradation, biodegradation, stability in water, and fugacity) was completed with data from a formal study, acceptable estimation modeling programs, and a technical discussion. As a result of its solubility in water and low volatility, fugacity estimations predict that TMPD will distribute primarily to soil and water. A technical discussion has been provided that indicates this compound is not likely to under go hydrolysis. The available biodegradation data indicate TMPD is likely to be readily degraded in the environment either by microbes found in wastewater systems or via hydroxyl mediated photo-oxidation. Environmental releases are limited as its primary use is in industrial applications as an intermediate in the synthesis of polymers.

The potential toxicity of TMPD to fish, Daphnia, and algae were determined through well-conducted studies that followed OECD guidelines or protocols that were very similar. The results of these studies demonstrate none of these organisms are sensitive species. The NOEC for daphnia and algae was >100 mg/L, while the LC_{50} for bluegill fish was >700 mg/L. A second much older study in various types of fish (catfish, rainbow and brown trout of various weights, and goldfish) saw no effects on mortality after 120 hours at 75 ppm in catfish, and following only an 8 hour exposure induced no mortalities at 750 ppm. Based on these data TMPD would not be classified according to the European Union's labeling directive and would correspond to a "low concern level" according to the U.S. EPA's assessment criteria. The potential for exposure to aqueous environments is unlikely due to its primary use as an industrial intermediate. Furthermore, TMPD is noted as being readily biodegradable.

The potential to induce toxicity in mammalian species following acute oral and inhalation exposures is very low. The oral LD_{50} value in rats was about 800-1,600 mg/kg, in mice the value was about 1,600-3,200 mg/kg, and in guinea pigs the value was about 1,800 mg/kg. Data from an inhalation study in rats showed no mortality following an acute 6 hour inhalation at 4,500 mg/m^3. TMPD was well tolerated with minimal evidence of toxicity following a 60-day dietary exposure at levels of 0.5 and 2% with a NOAEL of 0.5%. The only effects noted at the 2% level were a significant decrease in body weight in females and minor changes in some organ weights. However, hematological and clinical chemistries were all normal and no histomorphological alterations were noted in any tissue. Results from mutagenicity and chromosomal aberration studies indicate this material is not genotoxic. Developmental and reproductive toxicity endpoints were assessed simultaneously through the conduct of a developmental/reproductive toxicity screening study in rats. In this study, animals were fed TMPD at a dietary level of 1% for 3 generations. Results from this study indicate TMPD is not likely to induce either type of effect (NOAEL 1%).

In conclusion, an adequate assessment and summarization of all the Screening Information Data Set (SIDS) endpoints has been completed to satisfy the requirements of the HPV program without need for the conduct of any new or additional tests. This data set consists of results from studies conducted on TMPD that either followed established protocols under GLP assurances or scientifically acceptable procedures to assess the various endpoints. Where appropriate, some endpoints have been fulfilled through the utilization of data from modeling programs accepted by the EPA. The summarized data indicate that this chemical, when used appropriately, should constitute a low risk to workers and the general population as well as the environment.

EVALUATION OF DATA FOR QUALITY AND ACCEPTABILITY

The collected data were reviewed for quality and acceptability following the general US EPA guidance (3) and the systematic approach described by Klimisch *et al.* (4). These methods include consideration of the reliability, relevance and adequacy of the data in evaluating their usefulness for hazard assessment purposes. This scoring system was only applied to ecotoxicology and human health endpoint studies per EPA recommendation (5). The codification described by Klimisch specifies four categories of reliability for describing data adequacy. These are:

(1) Reliable without Restriction: Includes studies or data complying with Good Laboratory Practice (GLP) procedures, or with valid and/or internationally accepted testing guidelines, or in which the test parameters are documented and comparable to these guidelines.

(2) Reliable with Restrictions: Includes studies or data in which test parameters are documented but vary slightly from testing guidelines.

(3) Not Reliable: Includes studies or data in which there are interferences, or that use non-relevant organisms or exposure routes, or which were carried out using unacceptable methods, or where documentation is insufficient.

(4) Not Assignable: Includes studies or data in which insufficient detail is reported to assign a rating, e.g., listed in abstracts or secondary literature.

REFERENCES

1. EPIWIN, Version 3.10, Syracuse Research Corporation, Syracuse, New York.

2. US EPA. (1999). The Use of Structure-Activity Relationships (SAR) in the High Production Volume Chemicals Challenge Program. OPPT, EPA.

3. USEPA (1998). 3.4 Guidance for Meeting the SIDS Requirements (The SIDS Guide). Guidance for the HPV Challenge Program. Dated 11/2/98.

4. Klimisch, H.-J., Andreae, M., and Tillmann, U. (1997). A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data. *Regul. Toxicol. Pharmacol.* 25:1-5.

5. USEPA. 1999. Determining the Adequacy of Existing Data. Guidance for the HPV Challenge Program. Draft dated 2/10/99.